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Original Article

Actigraphic assessment of sleep/wake behavior in central disorders of hypersomnolence

Marco Filardi [a,*], Fabio Pizza [b,c], Monica Martoni [d], Stefano Vandi [b,c], Giuseppe Plazzi [b,c], Vincenzo Natale [a]

[a] Department of Psychology, University of Bologna, Bologna, Italy
[b] DIBINEM Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[c] IRCCS Istituto delle Scienze Neurologiche, Bologna, Italy
[d] DIMES Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

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ABSTRACT

Objective: To evaluate the reliability of actigraphy to distinguish the features of estimated daytime and nighttime sleep between patients with central disorders of hypersomnolence and healthy controls.
Methods: Thirty-nine drug-naïve patients with Narcolepsy Type 1, twenty-four drug-naïve patients with Idiopathic Hypersomnia, and thirty age- and sex- matched healthy controls underwent seven days of actigraphic and self-report monitoring of sleep/wake behavior. The following variables were examined: estimated time in bed (*e*TIB), estimated total sleep time, estimated sleep latency (*e*SOL), estimated sleep efficiency, estimated wake after sleep onset, number of estimated awakenings (*e*Awk), number of estimated awakenings longer than 5 minutes, estimated sleep motor activity (*e*SMA), number of estimated naps, mean duration of the longest estimated nap (*e*NapD), and daytime motor activity.
Results: All actigraphic parameters significantly differentiated the three groups, except *e*TIB and *e*SOL. A discriminant score computed combining actigraphic parameters from nighttime (*e*SMA, *e*Awk) and daytime (*e*NapD) periods showed a wide area under the curve (0.935) and a good balance between positive (95%) and negative predictive (87%) values in Narcolepsy Type 1 cases.
Conclusion: Actigraphy provided a reliable objective measurement of sleep quality and daytime napping behavior able to distinguish central disorders of hypersomnolence and in particular Narcolepsy Type 1. The nycthemeral profile, combined with a careful clinical evaluation, may be an ecological information, useful to track disease course.

1. Introduction

Narcolepsy Type 1 (NT1) and Idiopathic Hypersomnia (IH) are two central disorders of hypersomnolence characterized by chronic sleepiness not explained by altered nocturnal sleep or sleep deprivation [1]. Although hypersomnolence features may overlap in IH and NT1, these disorders display distinct clinical, neurophysiological, and biochemical presentations [2].

NT1 is characterized by daytime and nighttime symptoms: daytime sleepiness (hypersomnolence), with sleep attacks characterized by direct transitions into rapid eye movement (REM) sleep (sleep-onset REM periods – SOREMPs), cataplexy (sudden loss of muscle tone triggered by emotions), sleep paralyses, and hallucinations, and disrupted nighttime sleep [1,3]. Patients with NT1, indeed, present a nighttime sleep interrupted by numerous and prolonged awakenings, and also abnormal simple movements (e.g. nocturnal myoclonus) or complex behaviors (eg, parasomnias) during both REM and non-REM sleep [4]. Conversely, IH is characterized by hypersomnolence and nocturnal sleep with normal features and, possibly, long duration [1,5].

Nocturnal sleep and hypersomnolence are usually explored through nocturnal polysomnography (PSG) and multiple sleep latency test (MSLT) respectively. MSLT is the gold standard laboratory-based measure of daytime sleep propensity, currently used worldwide as main diagnostic tool for the differential diagnosis among central disorders of hypersomnolence [6,7].

Recently, several studies attempted a more naturalistic approach by comparing the features of spontaneous daytime sleep at 24-hour continuous polysomnography versus MSLT results, in the context of central disorders of hypersomnolence [8,9]. These studies emphasized the utility of prolonged recordings performed under conditions more similar to usual life habits of patients. Nevertheless, 24-hour recordings are difficult to apply to clinical practice.

Actigraphic monitoring has become, over the last two decades, a widely used assessment tool in sleep medicine to continuously

* Corresponding author. Department of Psychology, University of Bologna, Viale Berti Pichat 5, 40127 Bologna, Italy. Tel.: +39 051 2091846; fax: +39 051 243086.
E-mail address: marco.filardi@unibo.it (M. Filardi).

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document several nycthemeral cycles, barely interfering with a subject's daily routine [10,11].

According to the current International Classification of Sleep Disorders 3rd edition (ICSD-3), actigraphy plays a major role for the objective monitoring of sleep schedule and duration in the weeks prior to MSLT in central disorders of hypersomnolence in order to objectively rule out insufficient sleep or circadian rhythms misalignment [1]. Actigraphic studies on central disorders of hypersomnolence are rare, and the above ICSD-3 recommendations were mostly due to consensus [12], although preliminary data are of interest: Middelkoop and co-authors compared the circadian pattern of motor activity of 14 drug-free NT1 patients versus age- and sex-matched controls, and demonstrated that diurnal and nocturnal measures of "uninterrupted immobility" (defined as mean duration of periods without activity) were able to discriminate between groups, with NT1 patients showing a higher nocturnal motor activity profile [13]. More recently, Bruck and co-authors confirmed those findings, even though in a small cohort of NT1 patients ($n = 9$). Additionally, the authors showed that the actigraphic measurement of "immobility" could be successfully used to differentiate between medicated and unmedicated NT1 patients treated with wake-promoting drugs [14]. Finally, Poryazova and co-authors showed that actigraphic estimated sleep quality significantly improved after treatment with sodium oxybate, suggesting that actigraphy could offer a cheaper and simpler alternative to PSG for assessing sodium oxybate treatment effects [15].

The purpose of this study was to determine if actigraphy can reliably characterize the circadian profile of sleep and wakefulness of different central disorders of hypersomnolence and distinguish NT1 from IH patients and healthy controls by combining diurnal hypo-activity (as index of hypersomnolence) and nocturnal hyperactivity (as index of disrupted sleep quality) measures.

2. Materials and methods

2.1. Subjects

Subjects were patients evaluated for complaints of hypersomnolence, from March 2010 to January 2014, at the outpatient clinic for Narcolepsy of the Department of Biomedical and Neuromotor Sciences, University of Bologna, and who received a final diagnosis of central disorders of hypersomnolence according to the ICSD-3 criteria [1].

All patients underwent the following diagnostic protocol: (a) clinical evaluation performed by the same sleep specialist (G.P.); (b) assessment of subjective sleepiness by means of Italian version of the Epworth Sleepiness Scale (ESS) [16]; (c) seven days of actigraphic and self-report monitoring of sleep–wake behavior; (d) 48-hour continuous polysomnographic recording followed by (e) a MSLT with five nap opportunities; and (f) lumbar puncture to assay hypocretin-1 levels, where possible.

The final study sample included 63 patients, consisting of 39 NT1 patients (23 males, mean age 34 ± 16 years) and 24 IH patients (11 males, mean age 32 ± 15 years). All patients were drug-naïve at the time of actigraphic recording.

NT1 patients fulfilled the ICSD-3 criteria presenting: persistent daytime sleepiness (mean ESS score 16.41 ± 3.42), a clear-cut history of cataplexy ($n = 39/39$), and mean sleep latency <8 min (mean 3.14 ± 1.77) with at least two sleep-onset REM periods (mean 3.92 ± 1.10) at the MSLT. All patients were HLA DQB1*0602 positive and had reduced (ie, <110 pg/ml) or undetectable hypocretin-1 levels (mean 26.70 ± 27.72) when tested ($n = 24/39$).

IH diagnosis required the following criteria according to current ICSD-3: presence of persistent daytime sleepiness (mean ESS score 14.50 ± 3.57), absence of cataplexy, mean sleep latency <8 min (mean 6.14 ± 1.09) with fewer than two SOREM at MSLT (mean 0.38 ± 0.49) and nocturnal PSG, adequate schedule and duration of the main sleep period documented by actigraphy (estimated total sleep time = 417 ± 75 min.), and no evidence of concurrent sleep or medical disorder as stated by nocturnal PSG and clinical evaluation respectively. CSF hypocretin-1 concentration was in the normal range (ie, >200 pg/ml) in all patients tested ($n = 11$, mean 335.55 ± 138.03); four patients were HLA DQB1*0602 positive (16.6%).

Thirty healthy controls (15 males, mean age 29 ± 9 years) were recruited from the local community. Participants were clinically screened to rule out sleep or medical disorders; only subjects with regular sleep schedule and without complaints of sleep disturbance or daytime sleepiness (mean ESS score 4.47 ± 2.63) were included.

The study was approved by the local review board and all participants signed a written informed consent.

2.2. Actigraphic assessment

Actigraphy is based on small wrist-watch like devices that monitor movements for extended periods of time. Actigraphy is a semi quantitative method that provides an indirect assessment of sleep through the use of computerized scoring algorithms applied to the raw activity data.

The Micro Motionlogger® Watch actigraph (Ambulatory Monitoring, Inc., Ardsley, NY) was used in the present study. The hardware consists of a triaxial accelerometer; overall sensitivity is 0.01 g at the midpoint of bandpass filter which is set at 2–3 Hz, and sampling frequency is set at 32 Hz. This device also has case temperature and ambient light sensors. Actigraphs were initialized in zero crossing mode to collect data in 1-min epochs.

Actigraph data file were analyzed by Action W 2 – version 2.71 software (Ambulatory Monitoring, Inc., Ardsley, NY). This software identify each epoch as sleep or wake using the algorithm developed by Cole and co-authors [17]. The algorithm computed a weighted sum of the activity counts in the current minute, the preceding 4 minutes, and the following two minutes as follows: $S = 0.0033(1.06A_{-4} + 0.54A_{-3} + 0.58A_{-2} + 0.76A_{-1} + 2.3A_0 + 0.74A_{+1} + 0.67A_{+2})$, where A_{-4} to A_{-1} are the activity counts of the preceding 4 minutes, A_0 is the activity counts of the current minute, and A_{+1} and A_{+2} are the activity counts of the following 2 minutes. The current minute is scored as sleep when $S < 1$.

Participants were asked to wear the actigraph on the non-dominant arm over seven consecutive days, starting at the clinic visit, which are sufficient to obtain a meaningful description of the rest–activity behavior [18]. Subjects were instructed to maintain their habitual sleep/wake schedule during the recording period. Parallel to actigraphic assessment, subjects were asked to fill out a daily sleep log in which they would report: (i) what time they went to bed at night and their last awakening in the morning, and (ii) frequency and duration of diurnal naps. Moreover, subjects were instructed to push a button located on the side of the watch ("event marker") to mark occurrences such as time in and out of bed and periods when the actigraph was not worn. Event-marked points or sleep log information (if event-marked points were absent) were used in the editing procedure to identify sleep–wake periods and eliminate times of actigraphy removal.

2.3. Nighttime and daytime measures

For *nighttime period*, corresponding to the time between when the subject went to bed and switched off the light and final self-reported awakening in the morning, we considered the following actigraphic measures: estimated time in bed (*e*TIB – time in minutes, between reported light off and light on), estimated total sleep time (*e*TST – sum, in minutes, of all sleep epochs between light off and light on); estimated sleep onset latency (*e*SOL – interval in minutes,

between light off and sleep onset, the latter determined as the first epoch of a consecutive 20 minute period with no more than 1 minute of wake); estimated sleep motor activity (*e*SMA – mean number of movements within one minute, during sleep epochs); estimated wake after sleep onset (*e*WASO – sum, in minutes, of all wake epochs between estimated sleep onset and sleep end); and estimated sleep efficiency (*e*SE%, the ratio of TST to TIB multiplied by 100); estimated wake episodes (*e*Awk – number of epochs scored as wake between estimated sleep onset and sleep end) and number of estimated wake episodes lasting more than 5 consecutive epochs (*e*Awk >5).

For the *daytime period*, corresponding to the time between the final self-reported awakening in the morning and the beginning of a new major sleep period, we considered the following actigraphic measures: daytime motor activity (DMA – mean number of movements within one minute, during estimated wake period); number of estimated sleep episodes lasting more than 5 consecutive epochs (*e*Nap); and mean duration of longest estimated sleep episodes (*e*NapD – mean duration, in minutes, of the longest estimated sleep episodes).

2.4. Statistical analyses

Data for each group were explored using descriptive statistics (mean ± SD). Group differences in demographic and clinical data were analyzed with Pearson's chi-square test for categorical variables, Mann–Whitney test for ordinal data, and one-way between-group analysis of variance (ANOVA) for continuous variables.

Comparisons of actigraphic variables were performed by means of ANOVA, and post-hoc comparisons were performed using Bonferroni test.

A stepwise multiple discriminant analysis with Wilks's Lambda method was carried out to explore whether a set of variables is more effective in predicting group membership; F values of 3.84 for entry into, and 2.71 for removal from, the discriminant analysis were used. The first discriminant function selected was applied to the data and a receiver operating characteristic (ROC) curve was generated [19].

Values of the Area under ROC curves were used to select cut-off values; the Youden Index (ie, the higher value obtained calculating sensitivity+specificity-1) was used to determine optimal cut-off values; finally positive and negative predictive values were computed [20].

All statistical analyses were performed using SPSS 19.0 (SPSS, Inc. Chicago, Ill). *P*-value <0.05 was considered statistically significant.

3. Results

Chi-square and one-way ANOVA analyses revealed no differences among groups in either gender or age, respectively. One-way ANOVA showed no difference between NT1 and IH regarding levels of subjective sleepiness, while both clinical groups displayed higher ESS score than controls, as expected for inclusion criteria ($p < 0.0001$). Demographics, clinical, MSLT and biochemical data for all subjects are shown in Table 1. Overall the wearing time of actigraphic device exceeded 90% of the total recording time (mean values 95.40 ± 2.73%, range 90.21–99.13%). More in detail, the mean length in minutes of removal periods was 49.71 ± 30.13 for NT1, 49.97 ± 26.64 for IH and 42.66 ± 29.46 for controls, without significant differences among the three groups at univariate ANOVA ($F = 0.616$; $p = 0.542$).

Actigraphic nighttime and daytime data for the three groups are reported in Table 2, together with significance values of the ANOVA and post-hoc results. Results showed a main group effect for all actigraphic parameters considered except *e*TIB and *e*SOL. Post hoc contrast disclosed that: (a) NT1, IH and controls spent in bed the same amount of time, but NT1 patients slept significantly less than both IH and controls; (b) NT1 patients had the lowest *e*SE% with more time spent in *e*WASO than the other two groups; (c) NT1 patients showed the highest frequency of estimated nocturnal awakenings, followed by IH and controls respectively (NT1 > IH > Controls); (d) estimated nighttime motor activity levels of NT1 patients were significantly higher than those of IH and controls; (e) daytime motor activity levels of NT1 and IH patients were significantly reduced than those of controls; and (f) NT1 patients showed the highest frequency of daytime estimated naps, followed by IH and controls respectively. The same trend of differences was observed regarding average duration of the longest estimated nap (NT1 > IH > Controls). Stepwise discriminant analysis was performed including all variables that significantly differed among groups in the ANOVA.

The first function selected included three predictors *e*SMA, *e*Awk and *e*NapD that accounted for 97% of the explained between-group variance (Wilks's Lambda = 0.292, $p = 0.0001$, Eigenvalue = 2.228) and was computed as Discriminant Score (DS): SMA*0.049 + Awk*0.095 + NapD*0.04–2.934. Overall, this linear function correctly classified 81.7% of the cases. More in detail, classification accuracy was 87.2% for NT1 ($n = 34/39$), 58.3% for IH ($n = 14/24$), and 93.3% for healthy controls ($n = 28/30$) respectively. At ROC curve analysis, DS showed an area under the curve of 0.935 (Fig. 1); using a balanced approach, a cut-off of mean DS equal to

Table 1
Demographic characteristics, scale scores, and MSLT data of patients with narcolepsy type 1, idiopathic hypersomnia, and healthy controls.

	Narcolepsy type 1	Idiopathic hypersomnia	Healthy controls	*P*-value[a]
	$n = 39$	$n = 24$	$n = 30$	
	Mean ± SD (%)	Mean ± SD (%)	Mean ± SD	
Demographic and clinical data				
Age, years	34.21 ± 15.58	31.96 ± 15.20	29.37 ± 9.47	0.38
Male gender	23	11	15	0.56
BMI	27.20 ± 5.62	24.78 ± 4.43	22.79 ± 2.81	<0.001
ESS score	16.41 ± 3.42	14.50 ± 3.57	4.47 ± 2.63	<0.0001
CSF hypocretin-1	26.70 ± 27.72	335.55 ± 138.03		<0.0001
HLA DQB1*0602 positive	39 (100)	4 (16.6)		<0.0001
MSLT data				
MSLT sleep latency, minutes	3.14 ± 1.77	6.14 ± 1.09		<0.0001
SOREMs, numbers	3.92 ± 1.10	0.38 ± 0.49		<0.0001

BMI, body mass index; ESS, Epworth sleepiness scale; MSLT, multiple sleep latency test; SOREMP, sleep-onset REM period.
Data are presented as mean ± SD or number (percentage). Data were based on total number of subjects in each group, except CFS hypocretin-1, which included data from 24 (NT1) and 11 (IH) subjects, respectively.
[a] *P*-values were derived from One-way ANOVA, Chi-square test or Mann–Whitney U test, as appropriate.

Table 2
Actigraphic measures (Means and SD) and post-hoc results for NT1, IH and Control group.

	NT1 group ($n = 39$)	IH group ($n = 24$)	Control group ($n = 30$)	*P*-value	NT1 vs control	NT1 vs IH	IH vs control
	Mean ± SD	Mean ± SD	Mean ± SD		post-hoc/*t*-test	post-hoc/*t*-test	post-hoc/*t*-test
Nighttime period							
*e*TIB (min.)	471.04 ± 65.13	465.07 ± 85.59	478.82 ± 59.69	ns			
*e*TST (min.)	362.57 ± 83.49	417.41 ± 74.73	457.97 ± 53.04	<0.00001	0.0001	0.01	ns
*e*SOL (min.)	13.29 ± 13.34	11.53 ± 9.73	8.32 ± 4.68	ns			
*e*SE (%)	76.97 ± 13.97	89.65 ± 5.34	95.70 ± 1.99	<0.00001	0.0001	0.0001	ns
*e*WASO (min.)	92.50 ± 55.17	36.46 ± 26.68	12.49 ± 8.80	<0.00001	0.0001	0.0001	ns
*e*Awk (*n*°)	17.13 ± 6.90	11.95 ± 6.63	3.47 ± 2.13	<0.00001	0.0001	0.005	0.0001
*e*Awk >5 (*n*°)	5.18 ± 2.49	2.54 ± 2.10	1.20 ± 0.89	<0.00001	0.0001	0.0001	0.05
*e*SMA (counts)	29.80 ± 14.25	16.12 ± 6.21	9.98 ± 3.27	<0.00001	0.0001	0.0001	ns
Daytime period							
DMA (counts)	192.41 ± 30.26	199.14 ± 45.11	222.88 ± 15.94	<0.0005	0.0001	ns	0.05
*e*Nap (*n*°)	3.51 ± 1.67	2 ± 2.36	0.5 ± 0.90	<0.00001	0.0001	0.005	0.005
*e*NapD (min.)	35.46 ± 15.50	19.83 ± 17.38	6.40 ± 11.46	<0.00001	0.0001	0.0001	0.005
DS	1.57 ± 1.17	−0.22 ± 1.17	−1.86 ± 0.46	<0.00001	0.0001	0.0001	0.0001

SD, standard deviation; *e*TIB, estimated time in bed (min.); *e*TST, estimated total sleep time (min.); *e*SOL, estimated sleep onset latency (min.); *e*SE%, estimated sleep efficiency; *e*WASO, estimated wake after sleep onset (min.); *e*Awk, number of estimated awakenings; *e*Awk >5, number of estimated awakenings longer than 5 consecutive minutes; *e*SMA, mean estimated sleep motor activity (number of movements in one minute); DMA, mean daytime motor activity (number of movements in one minute); *e*Nap, number of daytime estimated sleep episodes longer than 5 consecutive minutes; *e*NapD, mean duration of longest estimated sleep episode (min.); DS, discriminant score.

−1.05 produced a good balance between positive (0.95) and negative (0.87) predictive values.

4. Discussion

This study was the first to investigate the actigraphic estimated daytime and nighttime sleep in a group of drug-naïve patients with different central disorders of hypersomnolence (namely NT1 and IH) and in healthy controls. Altogether, our findings showed that NT1 patients displayed a 24-hour actigraphic profile characterized by nighttime and daytime impairment, while IH patients displayed a daytime impairment without differences in overall estimated sleep quality when compared to healthy controls. The discrete daytime and nighttime actigraphic profile of patients suffering from central disorders of hypersomnolence suggests that actigraphy may provide useful information when combined with a careful clinical examination, and can also possibly distinguish among groups. Analyzing nighttime period we found that NT1 patients presented a marked decrease in estimated sleep quality, which was characterized by reduced estimated total sleep time with numerous estimated awakenings, extended time spent in *e*WASO and high representation of motor events, when compared with IH patients and controls. Conversely, patients with IH showed higher frequency of estimated nocturnal awakenings when compared with controls, without any other between-group difference. These results are in line with PSG studies in documenting the features of disrupted nighttime sleep in NT1 [4,21]. Noteworthy, levels of nocturnal motor activity rendered a different pattern in NT1, further confirming that an increased motor activity during night sleep is an intrinsic feature of this disease [22].

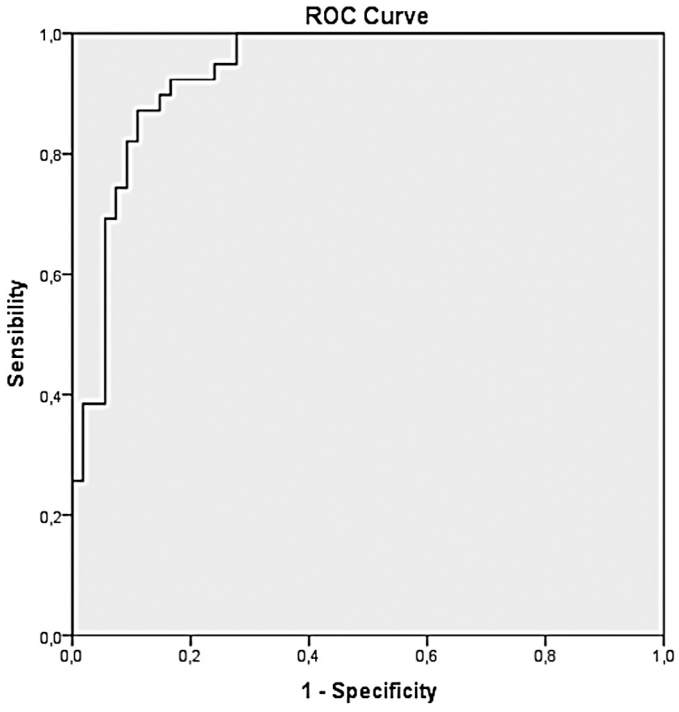

Fig. 1. Receiver operating characteristic curve for the combination (DS) of *e*Awk (number of estimated awakenings), *e*SMA (estimated sleep motor activity) and *e*NapD (mean duration of daytime longest estimated sleep episode).

Loss or impaired hypothalamic hypocretin (HCRT) signaling may, at least in part, explain the nighttime motor dysfunction of NT1 patients [23]. Hypocretin axons are found throughout the brain with dense projections to brainstem nuclei and to basal forebrain regions; under typical conditions hypocretinergic neurons promote motor activity during wakefulness and inhibit motor activity during REM sleep [24]. In patients with NT1 the opposite seems to take place, with motor inhibition and sleep occurring during the major wakefulness period, as well as enhanced muscle tone and motor activity during sleep [25].

During daytime patients with NT1 and IH present a more scattered distribution of estimated naps and a reduction in mean motor activity levels when compared to healthy controls. The nature and severity of diurnal impairment, however, differed among IH and NT1, with NT1 patients displaying highest estimated nap frequency and lowest motor activity level.

Our results confirm earlier studies that, however, considered different actigraphic variables (ie, immobility) and tested smaller groups of narcoleptic patients, reporting a trend in difference between NT1 and controls regarding the diurnal period [13,14]. In addition, by comparing patients with NT1 and IH, we extended these findings to other central disorders of hypersomnolence with comparable levels of subjective sleepiness, pinpointing that actigraphy may contribute to reliably render the features of daytime

behavior in different central disorders of hypersomnolence. Overall, we found that the actigraphic nycthemeral profile is able to reliably differentiate among groups. Moreover, it can be useful, in combination with PSG and MSLT, in both the diagnostic work-up of central disorders of hypersomnolence and in the follow-up as objective measures of disease course and treatments efficacy.

Noteworthy, we found that the combined use of both nocturnal (*e*SMA, *e*Awk) and diurnal (*e*NapD) parameters performed better in NT1 cases than any single actigraphic measure. Indeed, these parameters reflect two intrinsic features of NT1, namely, disrupted nocturnal sleep (*e*Awk, *e*SMA) and hypersomnolence (*e*NapD).

Some limitations of the present study should be acknowledged. First, although reporting on the largest actigraphic evaluation on NT1 patients in the literature, we are still underpowered to stratify the findings by different age groups. Second, some cautions need to be used in interpreting the diurnal motor activity data since DMA levels are clearly influenced by the scattered distribution and duration of sleep episodes during daytime. Future studies using chronobiological approach may help to establish whether the decrease in DMA levels still persists despite the elevated frequency of diurnal sleep episodes.

Overall, the present study shows that actigraphic monitoring is a useful technique to objectively assess the features of sleep–wake profile of central disorders of hypersomnolence, with the main advantage of providing more naturalistic information. Further studies are needed to explore whether the actigraphic measurements considered are sensitive enough to detect treatment effects on both nighttime and daytime sleep.

Disclosure of financial support and conflicts of interest

Marco Filardi, Fabio Pizza, Monica Martoni, Stefano Vandi and Vincenzo Natale have no financial interest to disclose and report no conflicts of interest; Giuseppe Plazzi participated in AB for UCB pharma and Jazz pharmaceuticals.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.08.017.

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